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CHAPTER 1

Introduction



ORTHOSTATIC HYPOTENSION

Orthostatic hypotension (OH) occurs frequently in the elderly population, and its prevalence increases with advancing age [1, 2]. OH is a decrease in blood pressure upon standing that reflects an impaired hemodynamic homeostasis. OH is defined by the International consensus as a decrease in systolic blood pressure (SBP) by at least 20 mmHg or a decrease in diastolic blood pressure (DBP) by at least 10 mmHg within 3 minutes after changing from supine to a standing position, ideally measured with a continuous blood pressure device [1]. In the few studies that reported the prevalence of OH in frail elderly nursing home residents, the prevalence varied between 18% and 50% [3-5]. In hospitalized elderly patients the prevalence of OH ranged from 8% to 67% [6, 7].

In healthy individuals, an active postural change triggers a baroreceptor-mediated response, which leads to an increase in heart rate, myocardial contractility, and peripheral vascular resistance in response to the shifting of a considerable amount of blood (300-800 ml) to the venous system below the diaphragm, mainly in the splanchnic venous system to the pelvis [7-12]. Stabilization of blood pressure is normally achieved within one minute [12].

OH occurs when baroreceptor-mediated autonomic responses are inadequate to maintain blood pressure on standing or because the blood volume is insufficient to support ventricular filling [7, 10]. The etiology of OH is multifactorial; decrease of baroreceptor sensitivity, pure autonomic failure, the use of different medications, hypovolemic disorders, and bed rest are all considered being possible causes of OH [6-8, 13, 14]. The normal age-related impairment of the baroreflex sensitivity, the higher prevalence of comorbidities, and the use of different medications are the main reasons for the higher prevalence of OH among elderly patients [7, 12]. OH can be accompanied by symptoms of cerebral hypoperfusion like light-headedness, dizziness, or syncope [1, 10, 12]. The amount of decrease in blood pressure is related to whether the patient experiences orthostatic complaints [12].

Baroreflex failure could also contribute to orthostatic hypertension (OHT) [15]. Next to OH, also OHT occurs more frequently in the elderly population [2]. OHT is an increase in blood pressure after orthostatic change. Although there is no official definition of OHT, many studies use an increase in SBP of 20 mmHg after postural change as a cut-off point. OHT can be considered as a form of prehypertension and is associated with hypertension-associated target-organ damage [15, 16].

MEASURING ORTHOSTATIC HYPOTENSION

According to the International consensus definition, active standing or the passive head-up tilt testing (HUT) and ideally continuous blood pressure measurements, instead of interval blood pressure measurements, are recommended to measure OH [1]. The HUT is a noninvasive tool for diagnosing syncope or orthostatic intolerance by rapidly moving the patient from a supine to an upright position [17]. Although interval blood pressure measurements to determine orthostatic hypotension are less accurate, automated sphygmomanometers are commonly used for this purpose in daily practice [18]. A previous study reported a lower prevalence of OH with the interval compared to the continuous blood pressure measurement device [19]. Due to these different results, concerns are raised against the threshold in the diagnostic criteria of OH and it is hard to apply the criteria on different blood pressure measurement devices in clinical practice.

Besides, orthostatic blood pressure is advised to be measured in standing position after 5 minutes of rest in supine position [1]. However, as many elderly patients are not able to stand during several minutes, sitting orthostatic blood pressure measurements are sometimes used as an alternative [20]. Only a few studies published results regarding OH in sitting position [21-23]; the prevalence of OH in these studies varied from 8% within community-dwelling individuals to 56% within elderly hospitalized patients [23]. It can be questioned whether orthostatic blood pressure measurements in the standing position can be replaced by measuring orthostatic blood pressure in the sitting position.

CLINICAL IMPLICATIONS OF ORTHOSTATIC HYPOTENSION

Some studies report that the presence of OH is related to an increased risk of cardiovascular disease and all-cause mortality in elderly people [24-27]. Besides, some studies suggest OH to be associated with falls, which in turn can lead to serious morbidity [28-30]. As the prevalence of OH in elderly is high, and associations with fall incidents were observed in these populations, OH may also be an important prognostic factor for chances of rehabilitation in nursing home patients. In the paragraphs below, the role of OH and hypertension in relation to different endpoints will be discussed.

Orthostatic hypotension and falling

Like the aetiology of OH, fall risk is a complex and multifactorial phenomenon and OH is one out of many risk factors believed to contribute to an increased fall risk in elderly people [30-32]. The combination of OH and other disabilities or medication usage may further impair orthostatic control and cause orthostatic complaints like syncope [30, 33, 34]. Especially the combination of OH and complaints has been identified as a cause of falls [30].

Two recent systematic reviews confirmed that OH is a risk factor for falling in elderly patients. However, the absolute attributive risk was not established due to the lack of a meta-analysis [30, 31]. Furthermore, studies that described the relationship between OH and falling have important limitations that need to be addressed; the lack of prospective fall data [35-37], not adjusting for important confounders [38], or not using the international consensus definition of OH [4]. These previous studies reported different results regarding the association with falling. Only the results regarding the relationship between recurrent falling and OH seem consistent; a twofold fall risk for patients with OH was described [4, 33]. Although most clinicians regard OH as a causal factor for falls, it thus remains highly uncertain whether and to what extent OH contributes to falling [31, 34].

Orthostatic hypotension and rehabilitation

The outcome of rehabilitation reflects the condition of the elderly patient and is a summation of many factors, including both physical and mental parameters [20, 39-46]. Also, OH and muscle strength are amongst the factors that have been found to influence rehabilitation in elderly patients [20, 43, 45]. As the prevalence of OH and low muscle strength is high in elderly patients and are considered as important risk factors for falling and frailty, these variables are likely to influence successful rehabilitation [29-31, 47-50]. As muscle strength and OH are probably related to successful rehabilitation, and possibly also interrelated, these factors should be combined (and adjusted for) in analysing their association with rehabilitation. If OH appears to be a prognostic factor for successful rehabilitation, clinicians should take OH into account, and should consider applying interventions aimed at reducing OH or orthostatic complaints.

Orthostatic hypotension and mortality

Previous studies reported that the presence of OH increases the risk of cardiovascular disease, cardiovascular mortality or all-cause mortality in elderly people [2, 14, 24-27, 31, 51-53]. Two meta-analyses were published regarding the relationship between OH and mortality [25, 54]. Both studies described that OH increased the risk of all-cause mortality, with risk ratios (RR) of 1.40 (95%CI 1.20-1.63) [25] and 1.50 (95%CI 1.24-1.81) [54]. However, an independent relationship can be questioned, since many included studies did not include important confounders in the relationship between OH and mortality [25]. In addition, it is questionable whether OH is a component of cardiovascular disease or an independent factor which increases mortality risk [54].

HYPERTENSION IN OLD AGE

Hypertension and using antihypertensive drugs are frequently mentioned as causal factors for OH in elderly patients [1, 12, 55, 56]. Although hypertension is a well-known risk factor for cardiovascular morbidity and mortality, it remains unclear whether hypertension is related to complications and death, and whether antihypertensive treatment is beneficial in old age. The Hypertension in the Very Elderly Trial (HYVET) was performed to investigate intensive blood pressure targets in elderly patients [57]. This study showed that elderly patients benefit from intensive antihypertensive treatment with a reduction in cardiovascular and all-cause mortality. The results of the HYVET study suggest strict treatment targets in elderly patients. However, the included patients in the HYVET study represent a highly selected population, and therefore the results cannot be extrapolated to the general elderly population but only to a very select group of vital elderly patients.

On the other hand, the relationship between blood pressure itself and mortality in old age has been investigated in many observational studies, and mostly inverse associations were reported [58, 59]. The observational PARTAGE study and the study of Askari et al. are the only studies that specifically investigated this relationship in nursing home populations. An inverse relationship was observed between SBP and mortality in the PARTAGE study [60, 61], while Askari et al. found no association between blood pressure and cardiovascular outcome [62].

At this moment, the intensity of antihypertensive treatment in individual elderly patients will have to be judged taking into account the degree of frailty, the estimated survival time, and the chances or presence of side effects of medication. Applying strict treatment targets to an elderly and frail population may lead to an increased prevalence of OH, and subsequently in an increased fall risk without any well-known benefits.

HEALTH-RELATED QUALITY OF LIFE

Comorbidities, depression, cognitive impairment and other geriatric syndromes are highly prevalent in old age and can greatly impact health-related quality of life (HRQOL) [63-68]. As a consequence, HRQOL is generally low in nursing home residents [64-66, 69-71]. Low HRQOL corresponds to substantial limitations in physical, emotional and social well-being due to a medical condition or its treatment [72].

The evaluation of HRQOL in individual patients can be used to measure disease-related distress and overall perception of health. Next to the evaluation of HRQOL as a separate outcome measure, HRQOL also has prognostic value in non-nursing home settings: a lower HRQOL has been associated with increased mortality risk, also in elderly patients [73].

HRQOL is also used to evaluate therapeutic interventions. Therefore, HRQOL measurement outcomes could have a variety of implications in decision-making processes regarding patients and medical interventions.

Measuring HRQOL in nursing home patients could lead to an increased understanding on factors that negatively impact HRQOL, ultimately aiming to improve HRQOL of this patient group. As mortality risk is already very high in old age, other clinical outcomes, like HRQOL may be more relevant.

AIM AND OUTLINE THESIS

In summary, OH is a decrease in blood pressure upon standing that reflects an impaired hemodynamic homeostasis. There is limited evidence about which methods to use to accurately determine OH, about the consequences when OH is established, and how to deal with OH in specifically the elderly population. It is advised to perform a continuous BP measurement, while automated sphygmomanometers with interval measurements are commonly used for this purpose in daily practice. Clinicians assume OH is causally related to falling or cardiovascular complications, despite the sparse evidence. The lack of evidence regarding OH underlines the need for gaining more knowledge about the implications of OH. Besides, information regarding mortality risk prediction of blood pressure in a nursing home population is lacking, while the need for strict antihypertensive treatment in this population is questionable. Finally, the role of HRQOL in this specific population seems important. It is unknown however, in what way it is related to cardiovascular morbidity and mortality.

The objectives of this thesis are to study the OH measurements itself, to study the clinical implications of OH in elderly patients, and to study factors (including OH) that are related to mortality and successful rehabilitation in nursing home residents.

In Chapters 2 and 3 various methods to measure OH are described. Firstly, a postural change from supine to standing position is compared with a change to sitting position. Secondly, continuous and interval blood pressure measurements are compared with each other. The hypothesis of this study is that measuring the blood pressure from supine to sitting instead of supine to standing leads to an underestimation of the prevalence of OH. This is possibly due to a difference in hemodynamic change in the standing versus the sitting position. When postural change is performed from supine to sitting, it is reasonable that less venous pooling in the legs will occur and a blood pressure drop will be observed less often, resulting in a lower prevalence of OH. The second hypothesis is that the prevalence of OH with the continuous blood pressure measurements would be higher compared to the interval blood pressure measurements.

In **chapters 4 and 5** the relationship between OH and falling is described. In **chapter 4**, the relationship between OH, first fall incident and recurrent falling in nursing home residents is prospectively investigated. A meta-analysis of prospective observational studies regarding this relationship is presented in **chapter 5**. The aim of the study is to investigate whether and to what extent orthostatic hypotension contributes to fall risk.

In **chapters 6 and 7** the relationship between OH and rehabilitation in elderly patients is described. In **chapter 6** the association between orthostatic hypotension, falling and successful rehabilitation in a nursing home population is investigated. The purpose of this study is to identify the prevalence of OH in frail elderly nursing home residents, and assess its association with falling and chances of successful rehabilitation. The hypothesis is that the presence of OH will negatively influence the time to successful rehabilitation. In **chapter 7** a study that aims to investigate the influence of OH and muscle strength on the chances of successful rehabilitation within elderly hospitalized hip fracture patients is described. Hip fractures are relatively common in frail elderly patients and associated with a high risk of morbidity and mortality [39, 43]. It is expected that OH is highly prevalent in hip fracture patients. This is caused by hip fracture-related factors like bed rest, surgery, inadequate water intake, and blood loss. The aim is to investigate the relation between OH, muscle strength and the chances of successful rehabilitation within elderly hospitalized patients.

The associations in the very elderly and frail patients between blood pressure, especially orthostatic changes in blood pressure, and mortality, are unclear. The relationship between orthostatic changes in blood pressure and mortality in a nursing home population is assessed in **chapter 8**. The aim is to investigate the association between blood pressure levels, an impaired hemodynamic homeostasis (OH and OHT) and mortality in nursing home patients. Furthermore, the additional value of OH and blood pressure in mortality prediction is assessed.

A cross-sectional study that investigates if the International consensus definition of OH is the best definition in relation with orthostatic complaints and falling is described in **chapter 9**. The relationship between different definitions of OH and orthostatic complaints and falling is explored.

In **chapter 10** the associations between HRQOL, rehabilitation and mortality in a nursing home population are described. The purpose of this study is to investigate the associations between HRQOL and two clinical relevant outcome measures; all-cause mortality and successful rehabilitation, in a nursing home population. Furthermore, the predictive capability of HRQOL on mortality is assessed.

Finally, in **chapter 11** I will discuss the different studies in this thesis. After the general discussion of this thesis, recommendations for daily practice and suggestions for future research are presented.

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